ORIGINAL ARTICLE

Sedation Depth During Spinal Anesthesia and the Development of Postoperative Delirium in Elderly Patients Undergoing Hip Fracture Repair

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OBJECTIVE: **To determine whether limiting intraoperative sedation depth during spinal anesthesia for hip fracture repair in elderly patients can decrease the prevalence of postoperative delirium.**

PATIENTS AND METHODS: **We performed a double-blind, randomized controlled trial at an academic medical center of elderly patients (≥65 years) without preoperative delirium or severe dementia who underwent hip fracture repair under spinal anesthesia with propofol sedation. Sedation depth was titrated using processed electroencephalography with the bispectral index (BIS), and patients were randomized to receive either deep (BIS, approximately 50) or light (BIS, ≥80) sedation. Postoperative delirium was assessed as defined by *Diagnostic and Statistical Manual of Mental Disorders (Third Edition Revised)* criteria using the Confusion Assessment Method beginning at any time from the second day after surgery.**

RESULTS: **From April 2, 2005, through October 30, 2008, a total of 114 patients were randomized. The prevalence of postoperative delirium was significantly lower in the light sedation group (11/57 [19%] vs 23/57 [40%] in the deep sedation group; *P*=.02), indicating that 1 incident of delirium will be prevented for every 4.7 patients treated with light sedation. The mean ± SD number of days of delirium during hospitalization was lower in the light sedation group than in the deep sedation group (0.5±1.5 days vs 1.4±4.0 days; *P*=.01).**

CONCLUSION: **The use of light propofol sedation decreased the prevalence of postoperative delirium by 50% compared with deep sedation. Limiting depth of sedation during spinal anesthesia is a simple, safe, and cost-effective intervention for preventing postoperative delirium in elderly patients that could be widely and readily adopted.**

Trial Registration: clinicaltrials.gov Identifier: NCT00590707

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BIS = bispectral index; CAM = Confusion Assessment Method; CI = confidence interval; ICU = intensive care unit; MMSE = Mini-Mental State Examination; NNT = number needed to treat; OR = odds ratio; PACU = postanesthesia care unit

Postoperative delirium occurs in elderly patients at an overall prevalence of 10% to 37%.[1,2] The prevalence ranges from 0% to 73%, depending on the study and type of surgery,[2] with a prevalence of 16% to 62% after hip fracture repair.[3-5] Although postoperative delirium usually resolves within 48 hours of onset,[6] delirium can persist and is associated with poor functional recovery, increased length of stay, higher costs, and greater likelihood of placement in an assisted living facility after surgery.[3,5,7-13] Therefore, interventions capable of reducing the occurrence of postoperative delirium would be important from a public health perspective, but relatively few proposed interventions have proven efficacious.[14-16]

Several demographic and perioperative variables are associated with postoperative delirium in elderly patients after hip fracture repair, the most important of which is preoperative dementia.[3,7,17-20] Other risk factors for postoperative delirium include age, systemic disease, functionality, and psychoactive medications.[3,19] Inhalational and intravenous anesthetics, opioids, benzodiazepines, and anticholinergic drugs are all known or suspected risk factors for postoperative delirium.[21-26] Although perioperative opioids are a risk factor for postoperative delirium, they are difficult to avoid after major surgery,[17,25] especially because undertreated pain may increase the risk of postoperative delirium.[17] Transfusion and perioperative medical complications may also be important.[3] Unfortunately, most of these risk factors are not readily modified at the time of surgery.

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Anesthetic technique is a potentially modifiable risk factor for postoperative delirium. Although administration of many drugs can be avoided or limited with regional anesthetic techniques and reductions in the prevalence of postoperative delirium have been observed with regional anesthesia, these results are inconsistent.[27,28] This inconsistency may be explained by reports that sedation levels consistent with general anesthesia are frequently observed during regional anesthesia[29-32] and, at least in an intensive care setting, that sedation level is an important risk factor for delirium.[23] The intravenous anesthetic propofol is commonly used to provide intraoperative sedation during spinal anesthesia and other regional anesthetics. Although

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propofol may have longer-term effects on some neurons of the central nervous system in vitro,[33] it is generally considered safe and without persistent aftereffects.

We hypothesized that minimizing sedation depth during spinal anesthesia for hip fracture repair in elderly patients could decrease the occurrence of postoperative delirium. Therefore, we performed a randomized controlled trial that compared the prevalence of postoperative delirium after hip fracture repair with spinal anesthesia with either deep or light propofol sedation.

PATIENTS AND METHODS

In a protocol approved by the Johns Hopkins Medicine Institutional Review Board, patients admitted to the multidisciplinary hip fracture service of the Johns Hopkins Bayview Medical Center who were 65 years or older and undergoing hip fracture repair with spinal anesthesia and propofol sedation were considered for inclusion in the study. Exclusion criteria were contraindications to spinal anesthesia (eg, clinically important aortic stenosis, coagulopathy, concurrent use of anticoagulants, spinal cord disease, refusal of spinal anesthesia), prior hip surgery, and mental or language barriers that would preclude data collection. Patients with severe congestive heart failure (New York Heart Association class IV) or severe chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease guidelines, stage III-IV)[34] were also excluded.

Study Protocol

On the day of surgery and after obtaining informed consent, we performed additional preoperative screening with the Mini-Mental State Examination (MMSE)[35] and the Confusion Assessment Method (CAM).[36] Patients with severe cognitive impairment (MMSE score, <15) were excluded to reduce the difficulty of demarcating delirium from dementia. Those with preoperative delirium as determined by positive CAM results were excluded because the goal of the study was to assess for postoperative delirium. Additional demographic and medical data were obtained, including comorbidities, medications, activities of daily living score,[37] instrumental activities of daily living score,[37,38] Inouye risk,[20] and other risk factors for delirium.[19,37] Patients were then randomized to receive deep or light sedation using a randomized block design with random length blocks. Randomization incorporated a stratification scheme for age (>80 years or 65-80 years) and cognitive impairment (MMSE score, 24-30 or 15-23).

Intraoperative monitoring consisted of blood pressure measurement by automatic cuff, pulse oximetry, 5-lead electrocardiography, and end-tidal carbon dioxide measurement. Bispectral index (BIS) monitoring of the electroencephalogram (BIS XP model and Quatro sensor electrode system; Aspect Medical System Inc, Norwood, MA) was initiated for all study patients on arrival to the operating room to assess the depth of sedation. Supplemental oxygen was provided with a nonrebreathing mask. Spinal anesthesia was administered with the patient in the lateral position with the fractured hip in the dependent position. In both study groups, sedation and analgesia for patient positioning and lumbar puncture were first achieved with either an intravenous propofol bolus or an intravenous midazolam bolus with optional intravenous fentanyl bolus. No more than 2 mg of midazolam was allowed for this purpose, and no additional midazolam was administered after initiation of spinal anesthesia. Spinal anesthesia was obtained by injecting 11.25 mg of 0.75% bupivacaine in solution with 8.25% dextrose solution (1.5 mL) into the subarachnoid space. Before surgical positioning, patients were maintained in the lateral position for at least 5 minutes after subarachnoid injection to intensify the block at the surgical site.

Sedation was provided during surgery by a propofol infusion targeted to a BIS of approximately 50 in the deep sedation group and a BIS of 80 or higher in the light sedation group. In general, these targets render patients in the deep sedation group unresponsive to noxious stimuli and those in the light sedation group responsive to voice.[39] Output from the BIS monitor was considered valid only for signal quality values of 95% or higher and electromyographic artifact values of 20 dB or lower. If patients in the light sedation group were comfortable without additional medication, the protocol did not mandate that they receive propofol. During the procedure, BIS readings and other intraoperative data were archived on a computer. If spinal block was judged by the attending anesthesiologist to be inadequate or of insufficient duration for the patient to tolerate surgery, a conversion to general anesthesia was made.

Any intraoperative systolic blood pressure decrease greater than 30% from preoperative values and/or systolic blood pressure less than 90 mm Hg was defined as hypotension and treated. The duration of hypotension as just defined was also recorded. The initial treatment regimen for hypotension included fluid bolus followed by phenylephrine by either bolus or infusion. Second-line drugs included glycopyrrolate or ephedrine, depending on the clinical circumstances and physician preference.

After surgery, patients were transferred to either the postanesthesia care unit (PACU) or the intensive care unit (ICU) at the discretion of the treating physicians. Postoperatively, analgesic therapy was standardized. Pain was initially controlled with intravenous bolus doses of hydromorphone. For those judged capable of using them by the PACU or ICU nursing staff, patient-controlled analgesic infusions of morphine sulfate provided analgesia. Otherwise, intravenous boluses of morphine sulfate were administered by the nursing staff. Intravenous analgesia was provided until patients were able to take oral medications. The switch to oral analgesics generally occurred on the first or second postoperative day (day 0 is the operative day), with the administration of oxycodone and acetaminophen, although tramadol was occasionally used.

Data were obtained throughout hospitalization on the severity of pain (measured on a 0-10 discrete scale), opioid administration, other medications, transfusion requirements, and complications. Delirium was assessed by CAM and the MMSE on the second postoperative day. Delirium was assessed daily by CAM from the third postoperative day until hospital discharge. All delirium assessments were conducted at approximately 10 AM by a trained research nurse (M.-R.B.). With the exception of the attending anesthesiologist of record, all study team members, including those assessing study outcomes, the patient and the patient's attending physician(s), were masked to treatment assignment. All study team members remained masked to outcome until data collection was completed after randomization of the last participant.

Statistical Analyses

The primary outcome variable was postoperative delirium according to CAM for any period during hospitalization from the second postoperative day onward. The study was powered by assuming a prevalence of postoperative delirium of 0.36 in the deep sedation group, similar to that observed after hip fracture repair in elderly patients under general anesthesia,[4] and a prevalence of 0.12 in the light sedation group, similar to that seen after knee replacement in elderly patients under epidural anesthesia with sedation.[40] On the basis of these assumptions, each group would require 49 patients to achieve a power of 0.80 at a significance level of .05. Several additional patients were included, assuming a 15% failure rate for the spinal anesthetic (inadequate block or duration). The use of all 57 patients in each group achieves a power of 0.86.

All data were analyzed by intention to treat. Frequency data were analyzed using the Fisher exact test or log-linear techniques, ordinal data were analyzed with the Mann-Whitney test, and continuous data were analyzed using analysis of variance. For continuous data with somewhat coarse sampling (eg, days of delirium and days in the ICU), nonparametric methods were used to confirm the reported significance levels. The likelihood of developing postoperative delirium was analyzed using logistic regression, with odds ratios (ORs) reported with their 95% confidence intervals (CIs). After identifying significant univariate predictors of delirium, we generated a multivariate model from the significant univariate predictors, which were variables that differed significantly between groups and those associated with postoperative delirium in other studies, and used a likelihood score to differentiate between models. Only variables that contributed significantly were incorporated into the model. A generalized linear model was then used to examine the determinants of the number of days of delirium experienced by the study patients. Unless otherwise indicated, frequency data are reported as the number and percentage of events, ordinal data are reported as median with upper and lower quartiles, and continuous data are reported as mean ± SD. The number needed to treat (NNT) was computed from frequency data, which yielded the probability of delirium in the deep sedation group ($0 \le P_D \le 1$) and light sedation group ($0 \le P_L \le 1$) so that $NNT = 1/(P_D - P_L)$. All *P* values reported are from 2-tailed tests. Differences were considered significant at $P<.05$. Statistical analysis was facilitated by Statistica software, version 6.0 (StatSoft, Tulsa, OK).

RESULTS

From April 2, 2005, through October 30, 2008, a total of 114 patients were randomized (Figure), with 57 patients in each arm. Demographic data (Table 1) are notable for the similarity of the 2 groups, particularly with respect to preoperative dementia and Inouye risk. Intraoperative data (Table 2) reveal the similarity of both groups with respect to the type of injury and associated repair. These data also demonstrate achievement of significant differences in BIS between the deep and light sedation groups that are consistent with the study design. These differences were accomplished with administration of significantly greater amounts of propofol to the deep sedation group throughout surgery and small but significantly greater amounts of midazolam to the light sedation group during placement of the spinal anesthetic. Duration of surgery was somewhat longer in the deep sedation group (P=.05). Conversion to general anesthesia was minimal (10/114 [9%]) overall and did not differ between groups (P=.74). Duration of intraoperative hypotension was not different between groups (P=.28) despite the greater amount of propofol administered to the deep sedation group.

The prevalence and mean days of delirium were significantly greater in the deep sedation group compared with the light sedation group (Table 3). Beginning on the second postoperative day, 23 (40%) of the 57 patients in the deep sedation group and 11 (19%) of the 57 patients in the light sedation group experienced at least 1 period of delirium (P=.02). This leads to an NNT of 4.7. Overall,

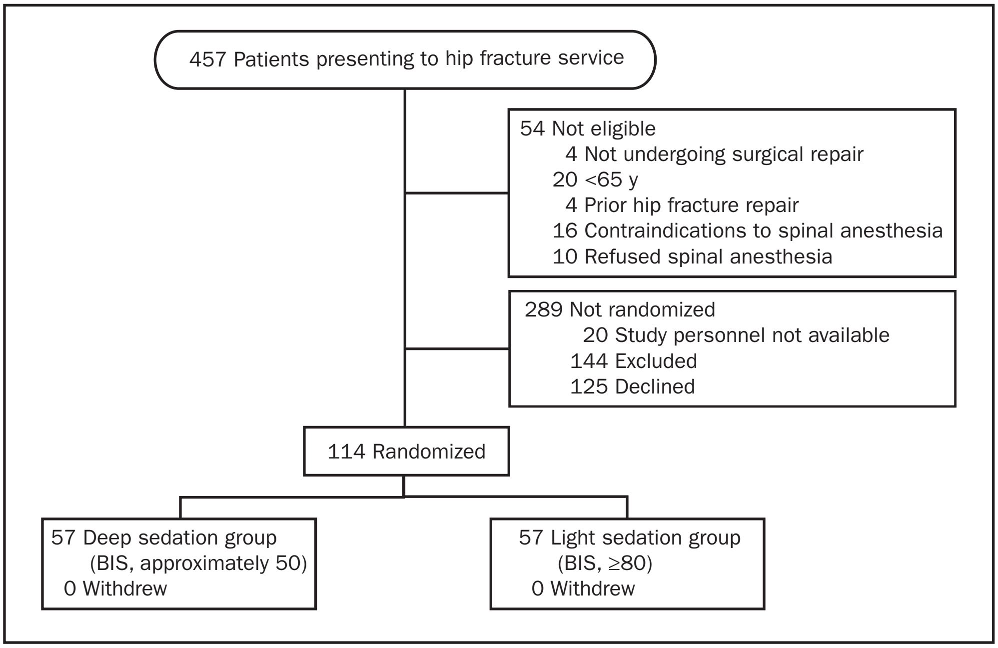

FIGURE. Study flow. The only contraindication to spinal anesthesia encountered was concurrent use of clopidogrel bisulfate at the time of injury. Patients were excluded from the study because they could not speak English (n=4), met exclusion criteria for dementia (Mini-Mental State Examination score, <15) preoperatively (n=42), met exclusion criteria for delirium (positive results on the Confusion Assessment Method) preoperatively (n=37), or simultaneously met the exclusion criteria for dementia and delirium (n=61). The indicated number of patients who declined to participate includes 1 who consented but withdrew before randomization. Although 4 patients in the deep sedation group and 6 in the light sedation group required conversion to general anesthesia because of incomplete or insufficient duration of spinal blockade, all data were analyzed on an intention-to-treat basis. BIS = bispectral index.

for the *entire* group, the mean number of days of delirium during hospitalization was greater for the deep sedation group (Table 3; *P*=.01). However, when considering *only* those for whom delirium occurred, duration of delirium did not differ between groups (Table 3; *P*=.77). For those with minimal preoperative cognitive impairment (MMSE score, ≥20), 14 (44%) of 32 patients in the deep sedation group and 5 (14%) of 35 patients in the light sedation group experienced postoperative delirium (*P*=.01). For those without cognitive impairment (MMSE score, ≥24), 11 (39%) of 28 in the deep sedation group and 3 (11%) of 27 in the light sedation group experienced postoperative delirium (*P*=.03). For these less cognitively impaired groups, the NNT is approximately 3.5.

In addition to group assignment, univariate predictors of postoperative delirium included average intraoperative BISs, preoperative dementia, preoperative MMSE score, mean number of units of packed erythrocytes transfused, experience of a postoperative complication, number of complications, admission to the ICU, and length of stay in the ICU (Table 4). Although preoperative activities of daily living scores were somewhat predictive of postoperative delirium, instrumental activities of daily living scores were not. Age, education level, duration of surgery, intraoperative propofol dose, duration of hypotension, and use of bone cement were not significantly associated with the development of postoperative delirium. Duration of sedation at a BIS of less than 50 was not predictive of the development of postoperative delirium (*P*=.05). To determine the relative contribution of the significant univariate predictors of postoperative delirium, we developed a multivariate model. Deep sedation (OR, 2.69; 95% CI, 1.04-6.93; *P*=.04), preoperative dementia (OR, 3.97; 95% CI, 1.54-10.2; *P*=.004), units of packed erythrocytes transfused (OR, 1.62; 95% CI, 1.10-2.38; *P*=.01), and admission to the ICU (OR, 3.69; 95% CI, 1.17-11.7; *P*=.02; where only those not already delirious were considered) were significant predictors of postoperative delirium (χ^2=26.2; *P*<.001). These variables were also significant when the number of days of postoperative delirium was considered. Except for admission to the ICU, these variables were also significant when the number of days of postoperative delirium was considered (*P*=.01 for deep sedation; *P*=.001 for preoperative dementia; *P*=.001 for number of units of erythrocytes transfused; *P*=.06 for admission to the ICU).

TABLE 1. **Demographic Characteristics of the Study Patients**[a]

Characteristic	Deep sedation (n=57)	Light sedation (n=57)	*P* value
Age, mean ± SD (y)	81.8±6.7	81.2±7.6	.71
Male/female, No.	14/43	17/40	.67
Weight, mean ± SD (kg)	66.6±17.0	62.1±14.8	.14
Height, mean ± SD (cm)	164±10	164±11	.96
ASA physical status score, median (lower-upper quartile)	3 (3-3)	3 (3-3)	.69
Education level, median (lower-upper quartile)[b]	3 (2-4)	3 (2-3.5)	.89
Mini-Mental State Examination score, mean ± SD (range, 0-30)	24.5±5.3	24.8±4.6	.78
Preoperative dementia[c]	21 (37)	19 (33)	.85
Depression	14 (25)	11 (19)	.65
Benzodiazepine use	2 (4)	3 (5)	>.99
Antidepressant use	10 (18)	9 (16)	>.99
Other psychiatric drug use	8 (14)	4 (7)	.36
Opioid use	4 (7)	2 (4)	.68
No. of systemic illnesses, mean ± SD (range, 0-7)[d]	1.4±1.4	1.6±1.2	.36
ADL, median (lower-upper quartile) (range, 0-6)	5 (5-6)	6 (5-6)	.48
Instrumental ADL, median (lower-upper quartile) (range, 0-8)	6 (3-8)	6 (5-8)	.29
Living independently[e]	32 (56)	42 (74)	.08
Inouye risk, median (lower-upper quartile) (range, 1-3)[f]	2 (2-2)	2 (2-2)	.91

[a] Data are No. (percentage) unless indicated otherwise. ADL = activities of daily living; ASA = American Society of Anesthesiologists.
[b] For education level, 1 indicates grade school; 2, some high school; 3, high school graduate; 4, vocational training or some college; 5, college graduate; 6, some graduate school; and 7, completed degree.
[c] As determined by clinical assessment or Mini-Mental State Examination score of less than 24.
[d] Coronary artery disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, chronic renal insufficiency or failure, chronic obstructive pulmonary disease, or malignant neoplasm.
[e] Lives in own home.
[f] For Inouye risk, 1 indicates low risk (0 points); 2, intermediate risk (1-2 points); and 3, high risk (3-4 points), in which 1 point is assigned for each of the 4 risk factors (visual impairment, severe illness, cognitive impairment, high blood urea nitrogen–creatinine ratio).[20]

TABLE 2. **Intraoperative Data for the Study Groups**[a]

Category	Deep sedation (n=57)	Light sedation (n=57)	*P* value
Time from arrival in emergency department until surgery, mean (SD) (d)	1.8 (1.42)	1.6 (1.5)	.52
Conversion to general anesthesia	4 (7)	6 (11)	.74
Duration of surgery, mean ± SD (min)	93±44	79±33	.05
Injuries, No.			>.99
Stable intertrochanteric fracture	9	10	
Unstable intertrochanteric fracture	14	17	
Stable femoral neck fracture	2	8	
Unstable femoral neck fracture	31	20	
Subtrochanteric fracture	1	2	
Surgical procedures, No.			>.99
Unipolar or bipolar implant	28	21	
Short or long intramedullary screw	24	25	
Screws	3	6	
Total hip arthroplasty	2	2	
Dynamic hip screw and plate	0	3	
Bone cement used in surgical repair	19 (33)	13 (23)	.30
Receiving propofol	57 (100)	52 (91)	.06
Propofol dose, mean ± SD (mg/kg)	10.2±5.6	2.5±2.7	<.001
Receiving midazolam	3 (5)	11 (19)	.04
Midazolam dose, mean ± SD (mg/kg)	1.26±6.36	5.53±12.42	.02
Receiving intraoperative opioids	46 (81)	46 (81)	>.99
Opioid use intraoperatively, mean ± SD (mg/kg)[b]	0.17±0.14	0.14±0.10	.26
Average BIS, mean ± SD (range, 0-100)	49.9±13.5	85.7±11.3	<.001
Average BIS <50, mean ± SD (min)	48±34	4±18	<.001
Duration of hypotension, mean ± SD (min)	13±22	9±14	.28
Intraoperative deaths	0 (0)	0 (0)	>.99

[a] Data are No. (percentage) unless indicated otherwise. BIS = bispectral index.
[b] Intraoperative fentanyl dose converted to its equivalent dose of intravenous morphine sulfate using 100 μg of intravenous fentanyl as equivalent to 10 mg of intravenous morphine sulfate.[41]

TABLE 3. **Hospitalization Data for the Study Groups**[a]

Category	Deep sedation (n=57)	Light sedation (n=57)	*P* value
Postoperative delirium	23 (40)	11 (19)	.02
Duration of delirium for all patients, mean ± SD (d)[b]	1.4±4.0	0.5±1.5	.01
Duration of delirium for those with delirium, mean ± SD (d)[b]	3.4±5.7	2.8±2.3	.77
Time from surgery until discharge, mean ± SD (d)	4.5±2.3	4.7±3.1	.69
Mini-Mental State Examination score on POD 2, mean ± SD (range, 0-30)	20.0±9.3	23.1±5.5	.08
Mini-Mental State Examination score on POD 2 vs preoperative score, mean ± SD	−4.4±6.1	−2.1±3.4	.06
Average pain on POD 1 to POD 3, mean ± SD (range, 0-10)	2.4±1.8	2.3±1.6	.80
Total postoperative opioid dose, mean ± SD (mg/kg)[c]	0.42±0.44	0.35±0.46	.41
Receiving erythrocyte transfusion	35 (61)	29 (51)	.35
Units of packed erythrocytes transfused perioperatively, mean ± SD	1.1±1.2	0.9±1.2	.31
Admission to intensive care unit at any time[d]	14 (25)	7 (12)	.15
Admission to intensive care unit without prior delirium[d]	12 (21)	7 (12)	.31
Duration of intensive care unit stay, mean ± SD (d)	1.0±2.3	0.4±1.4	.13
Patients with ≥1 complication(s)	30 (53)	26 (46)	.57
Patients with postoperative complications (range, 0-11)[e]	1.0 (1.8)	0.8 (1.4)	.44
Deaths during hospitalization	2 (4)	1 (2)	>.99

[a] Data are No. (percentage) unless indicated otherwise. POD = postoperative day.
[b] Data on duration of delirium are provided for both the entire population of each group and just those experiencing delirium in each group to determine if the course of delirium, once it occurs, differs between groups.
[c] All opioids converted to their equivalent dose of intravenous morphine sulfate using 100 μg of intravenous fentanyl, 2 mg of intravenous hydromorphone, 30 mg of oral oxycodone, and 150 mg of oral tramadol as equivalent to 10 mg of intravenous morphine sulfate.[41-43]
[d] Intensive care unit admission at any time during hospitalization whether patient delirious or not and those who were admitted to the intensive care unit in a nondelirious state.
[e] Postoperative complications averaged over the entire population of each group include the following: urinary tract infection, discharge with urinary drainage catheter, acute renal failure, pneumonia, congestive heart failure, myocardial infarction, new dysrhythmia, fall, return to surgery, pulmonary embolus or deep venous thrombosis, or wound infection.

DISCUSSION

This study shows that, in elderly patients undergoing hip fracture repair under spinal anesthesia with propofol sedation, the prevalence of delirium can be decreased by 50% with light sedation compared with deep sedation. This effect is associated with a mean reduction of almost 1 day of delirium for those in the light sedation group. These data show that, for every 4.7 patients treated in this manner, 1 incident of delirium will be prevented. For those with minimal preoperative cognitive impairment (MMSE score, ≥20) or those without cognitive impairment (MMSE score, ≥24), 1 incident of delirium would be prevented for approximately every 3.5 patients treated, indicating efficacy of the intervention even for those in these lower-risk groups.

Interpretation and generalizability of the study results require recognition that the targeted sedation level in the deep sedation group (BIS, approximately 50), although an electroencephalographic criterion often associated with general anesthesia,[39] is frequently observed during propofol sedation in elderly patients during spinal anesthesia for hip fracture repair[29] and other types of surgery.[31] Sedation levels that correlate with this electroencephalographic criterion[31] are also observed frequently during regional anesthetics and other procedures.[30,32] Therefore, the sedation criterion in the deep sedation group may be more representative of actual practice than generally appreciated. Although BIS is not always tightly linked to clinical end points,[44] its utility for titrating sedative levels of propofol is well supported.[45-47] However, the utility of BIS may vary, depending on the pharmacological features of the sedative drug.[48] Nevertheless, sedation end points used in the current study routinely occur during regional anesthesia and can be related to criteria used by clinical sedation scales, such as the Observer's Assessment of Alertness/Sedation Scale.[49]

The deep sedation group used significantly greater amounts of propofol compared with the light sedation group. Despite this association, propofol dose was not predictive of postoperative delirium. This finding suggests that the intraoperative sedation state itself rather than the amount of propofol administered was what contributed to the greater prevalence of delirium in the deep sedation group. The light sedation group received significantly greater amounts of midazolam than the deep sedation group. Because midazolam administration was permitted only during placement of the spinal anesthetic and was limited to no more than 2 mg, the increased use of midazolam in the light sedation group was small and likely represents efforts by the attending anesthesiologist to avoid deeper sedation in this group that could occur with a bolus of propofol during initiation of the spinal anesthetic. Regardless, given the association of delirium with benzodiazepine administration,[22] the small but greater use of midazolam in the light sedation group

TABLE 4. **Univariate Predictors of Postoperative Delirium**[a]

Variable	OR (95% CI)	χ^2 test	*P* value[b]
Deep sedation vs light sedation	2.83 (1.20-6.62)	6.13	.01
Average BIS	0.97 (0.954-0.995)	6.64	.01
Duration of surgery	1.007 (0.996-1.019)	1.73	.19
Duration BIS <50	1.011 (1.000-1.023)	3.70	.05
Age	1.045 (0.984-1.108)	2.19	.14
Preoperative dementia[c]	3.56 (1.52-8.32)	8.97	.003
Preoperative Mini-Mental State Examination score	0.86 (0.78-0.95)	10.76	.001
Education	0.84 (0.55-1.26)	0.80	.37
Preoperative ADL	0.72 (0.54-0.98)	5.09	.02
Preoperative IADL	0.88 (0.75-1.02)	2.96	.09
Living independently	0.70 (0.28-1.79)	0.55	.46
Inouye risk	0.66 (0.25-1.76)	0.73	.25
No. of systemic illnesses[d]	1.29 (0.94-1.75)	2.63	.11
Propofol dose	1.01 (0.95-1.09)	0.14	.71
Midazolam dose	0.97 (1.02-1.07)	0.92	.34
Duration of surgery	0.99 (0.98-1.00)	1.73	.19
Conversion to general anesthesia	0.61 (0.16-2.3)	0.52	.47
Use of bone cement	1.10 (0.45-2.69)	0.04	.84
Duration of intraoperative hypotension	0.99 (0.97-1.01)	0.49	.50
Erythrocyte transfusion	1.99 (0.85-4.66)	2.65	.10
Units of packed erythrocytes transfused	1.58 (1.12-2.22)	7.29	.007
≥1 Postoperative complications[e]	2.48 (1.07-5.75)	4.76	.03
No. of postoperative complications[f]	1.50 (1.08-2.09)	6.09	.02
Admission to intensive care unit without prior delirium[f]	8.19 (1.44-46.4)	5.86	.02
Length of intensive care unit stay	1.28 (1.02-1.59)	5.48	.02

[a] ADL = activities of daily living; BIS = bispectral index; CI = confidence interval; IADL = instrumental ADL; OR = odds ratio.
[b] As determined by univariate logistic regression, in which OR is given with respect to a unit change of the independent variable along with 95% CIs.
[c] As determined by clinical assessment or Mini-Mental State Examination score less than 24.
[d] Coronary artery disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, chronic renal insufficiency or failure, chronic obstructive pulmonary disease, or malignant neoplasm.
[e] Urinary tract infection, discharge with urinary drainage catheter, acute renal failure, pneumonia, congestive heart failure, myocardial infarction, new dysrhythmia, fall, return to surgery, pulmonary embolus or deep venous thrombosis, or wound infection.
[f] Considers just those admitted to the intensive care unit in a nondelirious state.

would have biased the study toward increased prevalence of delirium in this group.

Although the intraoperative sedation level was a modifiable risk factor for postoperative delirium, several demographic and perioperative factors were also associated with the prevalence of postoperative delirium in this study. These factors included preoperative dementia, perioperative erythrocyte transfusion, and admission to the ICU. Preoperative dementia is a documented risk factor for postoperative delirium[3,7,17-20]; thus, group assignment was stratified by MMSE score. The finding that erythrocyte transfusion and ICU admission are risk factors for delirium is not surprising given the results of other studies.[3,50] Because these factors are not controllable a priori, it is reassuring that no significant differences in these perioperative variables were found between treatment groups. Although duration of surgery was greater in the deep sedation group for unknown reasons, duration of surgery was not associated with an increased risk of postoperative delirium.

We determined the prevalence of postoperative delirium beginning on the second postoperative day using CAM. CAM is a delirium diagnostic instrument based on *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition Revised) criteria with a sensitivity and specificity of greater than 90% in elderly inpatient and outpatient cohorts[36] and leads to results similar to those from the direct application of *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition Revised) criteria.[51] Although other methods of delirium assessment exist, CAM is reliable in the perioperative period when used by trained personnel and is not excessively burdensome for a study that requires assessments on successive days of hospitalization.[52] Because CAM does not permit assessment of delirium subtypes, this information was not reported. Delirium assessment beginning on the second postoperative day was chosen to avoid any concern about lingering effects of anesthetic agents during the immediate postoperative period. Because delirium in the PACU predicts later postoperative delirium with 100% sensitivity and 85% specificity, some early episodes of postoperative delirium of short duration were almost certainly not observed in the current study.[4]

The mechanism whereby intraoperative sedation level affects the occurrence of postoperative delirium in elderly patients has not been elucidated. Hypotheses range from a cerebrovascular origin due to decreased perfusion associated with greater anesthetic depth in more deeply sedated patients, to toxicity of the larger doses of propofol administered to the deep sedation group, to a fundamental alteration in brain activity induced by deeper sedation. Data from the current study do not support a hemodynamic origin of postoperative delirium. Intraoperative blood pressure management was standardized to prevent blood pressure deviations that might affect postoperative cognition.[18,53] In addition, no differences were observed between treatment arms in the number of minutes that blood pressure deviated from the predetermined blood pressure criteria. Furthermore, the duration of hypotension was not an independent risk factor for postoperative delirium. The possibility of a toxic neural effect seems unlikely. Although the deep sedation group received higher doses of propofol, propofol dose itself was not an independent risk factor for postoperative delirium. By elimination, this finding suggests some drug-induced alteration in brain activity as the mechanism for the increased prevalence of postoperative delirium in the deep sedation group.

The neurobiologic mechanisms underlying delirium are not definitively understood, but several potential mechanisms have been hypothesized. The thalamus is the gateway for sensory input, the abnormal processing of which may characterize the hyperarousal of the delirious state.[54] Moreover, the thalamus is thought to play an important role in anesthetic-induced loss of consciousness[55]; intravenous and volatile anesthetics alter thalamic function, primarily through action at inhibitory γ-aminobutyric acid-mediated synapses[56-60]; and γ-aminobutyric acid-mediated tone is reduced with aging.[61] Furthermore, brief exposures of thalamic neurons to propofol may have longer-lasting effects.[33] The results of the current study are consistent with these more fundamental observations.

One limitation of the current study is the exclusion of patients with MMSE scores of less than 15, restricting the generalizability of the results to patients with at most moderate dementia. Furthermore, dementia assessment in this study might have been more reliable using a clinical consensus, rather than primary care physician diagnosis and the MMSE. It is already well established that preoperative dementia is a major risk factor for development of postoperative delirium,[3,7,17-20] which is consistent with the findings of the current study. Excluding those with severe dementia was necessary to recruit individuals who could fully participate in the study and whose dementia severity would not have obscured postoperative delirium assessment. Excluding patients with the most severe dementia may also have prevented the high likelihood of their developing postoperative delirium from masking benefits of the intervention. This concern is supported by the observation that those in the current study with higher MMSE scores were more likely to show a benefit of being in the light sedation group. Although data from this study do not indicate whether those with severe dementia or preoperative delirium would have benefitted from the intervention, there is no reason to believe that the intervention would have been harmful to these patients.

CONCLUSION

This study demonstrates in a population at high risk of developing postoperative delirium that undergoing hip fracture repair under spinal anesthesia with light sedation reduced the prevalence of postoperative delirium by 50% compared with deep sedation. These results were obtained by titrating propofol sedation depth using BIS-processed electroencephalography. Whether these results are relevant for other sedative drugs, other sedation end points, use of propofol during general anesthesia, and patients with more severe cognitive impairment than the study population awaits future investigation. This apparently safe and cost-effective intervention could prevent 1 case of delirium for every 4.7 patients treated and could be widely adopted with minimal difficulty in geriatric populations.

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